UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,682	11/10/2005	Bingxing Shi	0440/74021	5324

23432 7590 01/05/2011

COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1656	
MAIL DATE	DELIVERY MODE
01/05/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,682	SHI ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-12 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *10* is/are allowed.

6)☒ Claim(s) *1-5,7,8,11,12 and 15* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-5, 7-12 and 15 are pending.

Applicants' amendments filed November 16, 2009 and October 25, 2010 are acknowledged. Applicant's response has been fully considered. Claims 1-2, 4, 7-12 and 15 have been amended, and claims 6, 13 and 14 have been cancelled. Therefore, claims 1-5, 7-12 and 15 are examined.

Withdrawn Informalities

2. The previous objection to the specification regarding the amino acid and nucleotide sequences cited in the specification and Sequence Listing is withdrawn in view of applicants' amendment to the specification, applicants' submission of a new Sequence Listing and applicants' response in the amendments filed November 16, 2009 and October 25, 2010. CRF has been entered.

Withdrawn-Objection to New Matter Added to Specification

3. The previous objection to the supplemental amendment filed April 3, 2009 regarding introducing new matter into the disclosure is withdrawn in view of applicants' amendment to the specification, and applicants' response at pages 9-10 in the amendments filed November 16, 2009.

Withdrawn Claim Objections

4. The previous objection to claims 7-11 regarding citing amino acid sequences without providing a sequence identifier "SEQ ID NO:" is withdrawn in view of applicants' amendment to the claims, and applicants' response at page 10 in the amendment filed November 16, 2009.

Withdrawn Claim Rejections - 35 USC § 101

5. The previous rejection of claims 13 and 14 under 35 U.S.C. 101, is withdrawn in view of applicants' cancellation of the claim, and applicants' response at page 10 in the amendment filed November 16, 2009.

Withdrawn Claim Rejections - 35 USC § 112

6. The previous rejection of claims 8, 9 and 11 under 35 U.S.C. 112, first paragraph, new matter, is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 11-12 in the amendment filed November 16, 2009.

7. The previous rejection of claims 6, 13 and 14 under 35 U.S.C. 112, first paragraph, written description, is withdrawn in view of applicants' cancellation of the claims in the amendment filed November 16, 2009.

8. The previous rejection of claims 2, 4, 13 and 14 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claims, and applicants' response at pages 14-15 in the amendment filed November 16, 2009.

Withdrawn Claim Rejections - 35 USC § 102

9. The previous rejection of claims 6, 13 and 14, under 35 U.S.C. 102(b) as being anticipated by van Zyl et al. (Thrombosis Research 88, 419-426 (1997)), is withdrawn in view of applicants' cancellation of the claims in the amendment filed November 16, 2009.

10. The previous rejection of claims 6, 13 and 14, under 35 U.S.C. 102(b) as being anticipated by Dawson et al. (U.S. Patent 5,434,073), is withdrawn in view of applicants' cancellation of the claims in the amendment filed November 16, 2009.

11. The previous rejection of claims 12 and 15, under 35 U.S.C. 102(b) as being anticipated by Potter et al. (U.S. Patent 6,015,787), is withdrawn in view of applicants' amendment to the claims, and applicants' response at pages 19-20 in the amendment filed November 16, 2009.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-5, 7, 8, 11, 12 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, 7, 8, 11, 12 and 15 are directed to a fusion protein comprising a thrombolytic protein, an anticoagulant protein and a cleavable linker peptide recognized by blood coagulation factor, wherein the thrombolytic protein can be staphylokinase (SAK), tissue-type plasmingoen activator (t-PA), streptokinase (SK) , urokinase (UK), urokinase-like plasminogen activator (u-PA), and mutants thereof that activates other hemolytic factors or have thrombolytic activity, wherein the anticoagulant protein can be hirudin, antithrombin III, and mutants thereof; a method of preparing the fusion protein; a pharmaceutical composition comprising a fusion protein; and a method of treating a disease associated with thrombosis by administering the fusion protein.

In University of California v. Eli Lilly & Co., 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical

genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The specification indicates a fusion protein comprising a thrombolytic protein, an anticoagulant protein and a linker peptide, wherein the thrombolytic protein refers to the proteins having thrombolytic activity, e.g., staphylokinase (SAK), tissue-type plasmingoen activator (t-PA), streptokinase (SK), urokinase (UK), urokinase-like plasminogen activator (u-PA), and mutants thereof that activates other hemolytic factors or have thrombolytic activity, wherein the anticoagulant protein refers to proteins having anticoagulant activity, e.g., hirudin, antithrombin III, and mutants thereof, and wherein the linker peptide is a peptide recognized by blood coagulation factor; (page 4). However, the specification does not describe any mutant of a thrombolytic protein or an anticoagulant protein. While the specification provides specific examples of fusion proteins of SAK-GSIEGR-HV2, tPA-PRIEGR-HV2 and SAK-GSLGPR-

HV2 (Examples 1-3), the specification does not provide sufficient description for a genus of variants of the fusion proteins comprising various thrombolytic proteins, anticoagulant proteins and cleavable linker peptides when there is substantial variation in the whole genus of fusion proteins, which would encompass numerous embodiments. Since there is no structure-activity correlation for variants of thrombolytic proteins and anticoagulant proteins (e.g., mutants thereof), a skilled artisan cannot predict the structures of functional thrombolytic proteins and anticoagulant proteins. The lack of description on the structure-activity correlation for the variants of thrombolytic protein and anticoagulant protein and lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Response to Arguments

Applicants indicate that claim 1 has been amended to recite the linker peptide being recognized by blood coagulation factor, claims 2 and 4 to remove the term "venom", claims 12 and 15 to depend from claim 1, and claims 6, 13 and 14 have been canceled. Claim 2 recites the thrombolytic proteins such as staphylokinase (SAK), tissue-type plasmingoen activator (t-PA), streptokinase (SK) , urokinase (UK), urokinase-like plasminogen activator (u-PA); claim 4 recites the anticoagulant proteins such as hirudin and antithrombin III; and mutants of these proteins are still protein molecules and can be linked to either an anticoagulant protein or a thrombolytic protein to form a fusion protein. Applicants further indicate that based on the common knowledge in the art and the disclosures contained in the instant application, a person skilled in the art will appreciate that other thrombolytic proteins or anticoagulant proteins in

addition to those discussed in Examples 1-3, can also be used to form a fusion protein via the cleavable linker peptide to form a fusion protein. Accordingly, the present invention as stated in amended claims 1, 2, 4 and 11 would convey to one skilled in the art that inventors, at the time of the application was filed, had possession of the claimed invention (pages 12-14 of the response).

Applicants' response has been fully considered. However, the arguments are not found persuasive because of the following reasons. While the specification provides three specific fusion proteins (SAK-GSIEGR-HV2, tPA-PRIEGR-HV2 and SAK-GSLGPR-HV2; Examples 1-3) and discloses some thrombolytic proteins such as staphylokinase (SAK), tissue-type plasmingoen activator (t-PA), streptokinase (SK) , urokinase (UK), urokinase-like plasminogen activator (u-PA), and some anticoagulant proteins such as hirudin and antithrombin III, the specification does not provide sufficient description for a genus of variants of fusion proteins comprising various thrombolytic proteins, anticoagulant proteins and cleavable linker peptides, which would encompass numerous embodiments in the whole genus of fusion proteins when there are no structures defined in thrombolytic proteins and anticoagulant proteins. Furthermore, there is no structure-activity correlation for variants of thrombolytic proteins and anticoagulant proteins (e.g., mutants thereof), a skilled artisan cannot predict the structures of functional thrombolytic proteins and anticoagulant proteins. The lack of description on the structure-activity correlation for variants of thrombolytic protein and anticoagulant protein as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention. Therefore, the rejection is maintained.

Maintained Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-5, 7 and 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by van Zyl et al. (Thrombosis Research 88, 419-426 (1997)).

van Zyl et al. teach the production of recombinant antithrombotic and fibrinolytic protein, PLATSAK in E. coli, wherein the PLATSAK gene comprises staphylokinase, fused via a cleavable linker by FXa to an antithrombotic peptide of 29 amino acids comprising RGD sequence, a part of fibrinopeptide A and the tail of hirudin, and wherein the purified protein has antithrombin activity, antiplatelet activity and fibrinolytic activity (Abstract; Figs. 1 and 2; page 422; claims 1-5, 7 and 11-12).

Response to Arguments

Applicants indicate the fusion protein disclosed by van Zyl et al. is aimed to treatment for thrombosis with less hemorrhagic side effects. However, the fusion protein of van Zyl et al. significantly lengthened aPTT and TT values (van Zyl et al., p. 423) which reveal the risk of hemorrhagic side effects. Additionally, van Zyl et al. do not state the mechanism of interaction of the fusion protein with thrombin and provide no data to show whether the antithrombin activity is due to the hirudin or the fibrinopeptide A components (van Zyl et al., p. 423). Moreover, to treat thrombosis with less hemorrhagic side effects, the fusion protein itself should be with less hemorrhagic effect and should be activated by cleavage by factor Xa or thrombin

quickly into functional components to exert the therapeutic effect. However, many experiments have demonstrated that there are troubles associated with the use of thrombin or factor Xa to cleave fusion proteins. For instance, there is no evidence to prove that the linker site in any fusion proteins can be successfully cleaved by thrombin or factor Xa (See Raftery et al. (1999); Muse et al. (1999); Belmouden et al. (1993); Ko et al. (1993); Sharma et al. (1995); Wang et al. (1999)). Furthermore, Van Zyle et al. did not test the cleavage of the fusion protein PLATSAK by factor Xa and suggested that it was not cleaved (van Zyl et al., p.425, left column, lines 22-24). Accordingly, applicants maintain that van Zyl et al. do not anticipate applicants' claimed invention as recited in amended claims 1 and 11 (pages 15-17 of the response).

Applicants' response has been fully considered. However, the arguments are not found persuasive because of the following reasons. First, van Zyl et al. teach the production of recombinant antithrombotic and fibrinolytic protein, PLATSAK in E. coli, wherein the PLATSAK comprises staphylokinase (i.e., a thrombolytic protein), fused via a cleavable linker by FXa to an antithrombotic peptide of 29 amino acids (i.e., an anticoagulant protein; Fig. 4) comprising RGD sequence, a part of fibrinopeptide A and the tail of hirudin, which meets the criteria of the claimed fusion protein. Secondly, aPTT and TT (Fig. 4) are standard coagulation assays and the fusion protein of van Zyl et al. that lengthened aPTT and TT values shows its anticoagulant and antithrombotic activity. Third, since SAK had no effect on TT and aPTT, the lengthening in TT and aPTT (anticoagulant activity) must therefore be due to the two antithrombin sequences present in the peptide fused to SAK (page 423, right column, second full paragraph). Although van Zyl et al. do not state the mechanism of interaction of the fusion protein with thrombin, the PLATSAK markedly lengthened the aPTT and TT (Fig. 4) and

inhibited the amidolytic activity of thrmobin (Fig 5) when compared to equimolar concentrations of the antithrombin part of fibrinopeptide A and the tail of hirudin, which strongly suggests the combination of the fibrinopeptide A part and the hirudin-tail with SAK greatly enhances the antithrombin activity of PLATSAK (page 424, left column, second full paragraph). Therefore, the fusion protein of van Zyl et al. can be used for a pharmaceutical composition (page 425, last paragraph). While Van Zyl et al. did not test the cleavage of the fusion protein PLATSAK by factor Xa, the fusion protein of Van Zyl et al. contains a cleavable linker peptide recognized by factor Xa, which meets the limitation cited in the instant claims. Therefore, van Zyl et al. anticipates claims 1-5, 7 and 11-12.

14. Claims 1, 2, 4-5, 7, 11, 12 and 15 rejected under 35 U.S.C. 102(b) as being anticipated by Dawson et al. (U.S. Patent 5,434,073, published on 7/18/1995).

Dawson et al. teach the production of fusion proteins by linking together fibrinolytic (e.g., streptokinase) and/or anti-thrombotic protein (e.g., hirudin) with a cleavable linker (factor Xa (IEGR) or thrombin cleavage site (X-PR)), their preparation, pharmaceutical compositions comprising the fusion proteins and their use in the treatment of thrombotic diseases (column 1, lines 11-16; columns 2-5; claims 1, 2, 4-5, 7, 11, 12 and 15), e.g., construction of a vector for the expression of hirudin-IEGR-streptokinase fusion gene (Examples 8, 9) and expression of streptokinase-IEGR-hirudin fusion gene and hirudin-IEGR-streptokinase (Examples 14-15).

Response to Arguments

Applicants indicate the fusion protein disclosed by Dawson et al. is aimed to treatment for thrombosis with less hemorrhagic side effects. However, the fusion protein of Dawson et al. does not clearly indicate the time required for cleavage by factor Xa of a hirudin-IEGR-hirudin

fusion protein (Example 3) and indicates the time required for cleavage of a streptokinase-streptokinase fusion gene by thrombin was 14 hours, which is far too long to be able to exert thrombolytic effect as a therapeutic drug. Additionally, data for cleavage of Streptokinase-IEGR-Hirudin (Example 14) and Hirudin-IEGR-Streptokinase (Example 15) were not listed, and therefore do not indicate that the cleavage effect was positive for this particular fusion protein construct. Moreover, Dawson et al. do not indicate the behavior of the fusion protein in an in vivo experiment. Furthermore, to treat thrombosis with less hemorrhagic side effects, the fusion protein itself should be with less hemorrhagic effect and should be activated by cleavage by factor Xa or thrombin quickly into functional components to exert the therapeutic effect. However, many experiments have demonstrated that there are troubles associated with the use of thrombin or factor Xa to cleave fusion proteins. For instance, there is no evidence to prove that the linker site in any fusion proteins can be successfully cleaved by thrombin or factor Xa (See Raftery et al. (1999); Muse et al. (1999); Belmouden et al. (1993); Ko et al. (1993); Sharma et al. (1995); Wang et al. (1999)). Dawson et al. did not test the cleavage of a Streptokinase-IEGR-Hirudin or a Hirudin-IEGR-Streptokinase by factor Xa or by thrombin, and suggested that the fusion protein that was cleaved by thrombin took 14 hours to cleave, which would prevent it from working as a therapeutic drug. Accordingly, applicants maintain that Dawson et al. do not anticipate applicants' claimed invention as recited in amended claims 1 and 11 (pages 17-19 of the response).

Applicants' response has been fully considered. However, the arguments are not found persuasive because of the following reasons. First, Dawson et al. teach the production of fusion proteins by linking together fibrinolytic (e.g., streptokinase) and/or anti-thrombotic protein (e.g.,

hirudin) with a cleavable linker (factor Xa (IEGR) or thrombin cleavage site (X-PR)), e.g., expression of streptokinase-IEGR-hirudin fusion gene and hirudin-IEGR-streptokinase (Examples 14-15), which meets the criteria of the claimed fusion protein. Secondly, while Dawson et al. did not test the cleavage of a Streptokinase-IEGR-Hirudin or a Hirudin-IEGR-Streptokinase by factor Xa or by thrombin, and suggested that the fusion protein that was cleaved by thrombin took 14 hours to cleave, the fusion protein of Dawson et al. contains a cleavable peptide recognized by thrombin or factor Xa, which meets the limitation of the claimed fusion protein. Furthermore, the claimed fusion protein merely indicates it contains a blood coagulation factor cleavage site, it does not indicate the cleavage of fusion protein by the blood coagulation has to be quick. Therefore, Dawson et al. anticipates claims 1, 2, 4-5, 7, 11, 12 and 15.

Claim objections

15. Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

16. Claims 1-5, 7-8, 11, 12 and 15 are rejected; and claim 9 is objected to. It appears that claim 10 is free of art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached at 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK
January 3, 2011